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Towards a mathematical theory of rTMS-induced neural plasticity

Stimulation of the brain and nervous system with electrical and magnetic fields, for both therapeutic and scientific purposes, has been at the beating heart of the field of Clinical Neurophysiology since its earliest days (Fields, 2020). The past century has seen a considerable amount of focused research, technological innovation, and clinical protocol development in this area. It remains the case, however, that we lack a complete – or arguably even an adequate – understanding of what happens 'under the hood' when a given brain region is stimulated, with a given modality (e.g. transcranial magnetic, direct current, alternating current, temporal interference, or focused ultrasound stimulation [TMS/TDCS/TACS/TTIS/TFUS], deep brain stimulation [DBS], electro/magnetoconvulsive therapy [ECT/MST]), for a given temporal pattern (e.g. waveform shape, frequency/burst/pulse structure; intermittency, duration, acceleration, etc).

The exact contours of what might count as an adequate understanding here is a complex question with no simple single answer. Any answer to it should nevertheless follow a few minimal criteria, namely that it should draw on a *theory* of the (observable neurostimulation) phenomenon in question that is i) neurobiologically explanatory, ii) empirically predictive, and iii) mathematically expressed. The final criterion, of being a theory that can be written down in equations, is typically not as strictly necessary for successful theories in biology as it is in the physical sciences. However, the goal of improving the precision and clinical effectiveness of brain stimulation technologies has several associated challenges that necessitate use of numerical simulation techniques, which in turn require that the theory can be expressed in mathematical model form. Chief amongst these challenges is the profoundly difficult problem of how to explore the vast space of potential protocol parameters available for any given stimulation modality/device, much of which remains uncharted territory (Caulfield & Brown, 2022). The number of points in these spaces (such as, for example, the space of possible clinically-viable rTMS protocols) is usually somewhere between unfathomably high and countably infinite.

These are, suffice to say, very large numbers. However, the specific difficulty that they pose is not that the potential protocol space is large per se, but the resources (time, money, infrastructure) it would take to map it comprehensively using experimental means alone. 'Mapping the space' here is also a somewhat fuzzy concept. Ultimately from a translational perspective, alternative protocols would ideally be characterized in terms of therapeutic clinical trial outcomes. An oft-used proxy to this is 'target engagement' in healthy non-patient populations, or just the strength of any primary physiological effects, such as the direction and strength of induced plasticity responses.

In fact, this issue does not even need very large combinatorial explosions to become problematic: comprehensively mapping even very restricted subsets of reasonable stimulation protocol parameters is well beyond the capacity of current experimental approaches. Consider, for example, a hypothetical study in healthy human subjects examining intermittent theta burst stimulation (iTBS) – a well-established TMS protocol for which (some of) the standard parameter set of 3 pules-per-burst, 5 Hz carrier (theta) frequency, 2 s ON-period, 8 s OFF-period (Huang et al., 2005), has been extensively used in research and clinical contexts, including FDA-approved therapies for treatment-resistant major depression (Blumberger et al., 2018; Cole et al., 2022) and other indications. In this hypothetical study, if just two additional settings are added for each of these four iTBS parameters (so 2/3/4 pulses-per-burst, 4/5/6 Hz carrier frequency, 1/2/3 s ON-periods, 7/8/9 s OFF-periods), each participant would need to attend $3 \times 3 \times 3 \times 3 = 81$ sessions. In healthy-control neurophysiology experiments, these would typically be 2–3 h in-lab sessions. If this were an accelerated-design TMS clinical trial (where each protocol is applied clinically not just for a single session but multiple times a day intensively over several days), it would correspond to patients receiving a 9am-5pm neurostimulation therapy in a hospital or clinic every day for over a year.

The important point to emphasize in this hypothetical example is that this experiment would be a modest, if not positively spartan selection of protocol variants, given the full space of possible combinations. Moreover, the fact that such a modest selection generates such a laughably impractical experimental design (which, to be clear, can and will never actually be done) underscores the need for numerical simulation approaches, which aim to provide *in silico* analogues of the aforementioned lab-based human neurophysiology experiments. Such simulated experiments are virtually instantaneous and highly (embarrassingly) parallelizable, which means for example that an afternoon of *in silico* experimentation can cover orders of magnitude more territory (in terms of parameter configurations, such as the iTBS protocol variants discussed above) than the entire history of the experimental neurostimulation research. This is useful not only for exploring the virgin territory of seldom- or never-tried stimulation protocols, but also for the well-mapped territory of standard protocols with minor adjustments and optimizations for individual patients, such as using individual structural and functional neuroimaging data or real-time closed-loop feedback from concurrent neurophysiological recordings (Zrenner & Ziemann, 2024).

The critical ingredient needed to realize this exciting future of personalized, precision neurostimulation therapeutics is – returning to our earlier point – an adequately explanatory, predictive, and computationally implementable theory of how the stimulation modality in question modulates and/or modifies brain physiology. This theory should include, at its chosen level of granularity, the mechanism of

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action, dependence on stimulation protocol parameter values, and measurable short/long-term effects of a given candidate protocol.

So, what is the current status of mathematical theories – specifically of rTMS-induced neural plasticity – that might in the near future provide a robust basis for this kind of *in silico* therapeutic protocol exploration and optimization? The article by Ma et al. (2025) in this issue of Clinical Neurophysiology offers some important new perspectives and novel results on this topic, as well as providing an excellent summary of the current state-of-the art and key prior work to date.

Key exponents in this line of theoretical neuroscience research over the past two decades include Ying-Zu Huang (Huang et al., 2011), Peter Robinson, Felix Fung (Fung & Robinson, 2013, 2014), Marcus Wilson (Wilson et al., 2016, 2018, 2023), and more recently Ke Ma and colleagues (Ma et al., 2022, 2025), much of which builds on foundational understanding of neural plasticity from earlier contributors such as (Shouval et al., 2002; Yeung et al., 2004), Bienenstock (Bienenstock et al., 1982), and others. The basic objective pursued in this work is to develop models that accurately describe the net effect of one or other multi-minute rTMS stimulation protocol, such as conventional intermittent/continuous (i/c)TBS, administered for a certain amount of time or number of pulses. Given the limited spatial focality and relatively slow-acting nature of rTMS, the typical approach is to use a type of neural model broady known as a *rate-based neural population* (or neural mass) *model*. The level of description is thus coarse-grained in both time (i.e. millisecond-level temporal precision is not required), and space (i.e. single neuron-level precision not required). It also intentionally leaves out other parts of the full complex causal chain of what happens 'under the cranial hood' in response to TMS, such as the primary biophysical response (how secondary electrical currents generated by TMS propagate through brain tissue) and the primary physiological response (how neurons and local/large-scale polysynaptic neural circuits are activated by these secondary electrical currents). The first of these is reasonably well-understood by electromagnetic field theory under quasi-static approximations, for which well-established frameworks exist from engineering and computational physics using finite-element modelling and numerical simulations (Aberra et al., 2020; Dannhauer et al., 2022; Thielscher et al., 2015). The second is also reasonably well-understood in outline, as involving generation of action potentials and an evoked response in local networks for fast responses (Schaworonkow and Triesch (2017); Triesch et al., 2015), and larger-scale networks for slower whole-brain responses (Momi et al., 2023). Also intentionally left out from the framework adopted by Ma et al. are short-term plasticity mechanisms and phenomena, such as neural adaptation, spike timing-dependent plasticity, and in the TMS context experimental phenomena such as short/long interval intracortical inhibition (S/LICI).

Overlooking these other more immediate stimulus-evoked aspects of the TMS response allows for a focus on what is arguably the most interesting, probably the most clinically relevant, and certainly the most enigmatic aspects of TMS neurophysiology: the slow stuff. The common understanding is that rTMS and related modalities engage the same well-characterized synaptic plasticity mechanisms underlying the phenomena of long-term potentiation (LTP) and long-term depression (LTD) regularly observed in experimental (slice / in vitro) electrophysiology research (Huang et al., 2005, 2017; Larson & Munkácsy, 2015). Whilst the experimental effects of interest here can be subtle, complex, and often highly variable (Fitzgerald et al., 2016; Ozdemir et al., 2021; Park, 2022), there are several well-replicated canonical phenomena and experimental outcomes, usually quantified in terms of measured pre vs. post rTMS changes to (single-pulse TMS) motor-evoked potential (MEP) amplitudes measured from the hand muscles. The most well-known of these are excitatory/facilitatory effects with iTBS and high-frequency ($\geq$10 Hz) rTMS, and inhibitory/suppressive effects with cTBS and low-frequency ($\leq$1Hz) rTMS. Of particular interest to Ma et al. in their new work are the rather striking observations of temporally complex plasticity response profiles extending over tens of minutes during and following rTMS administration, including slowly-rising after-effects – whereby plasticity effects are maximal 20–30 min after the TMS, and plasticity sign inversion – whereby effects switch from LTP-like to LTD-like changes over increasing pulse numbers (Fung & Robinson, 2014; Gamboa et al., 2010; Wilson et al., 2018).

So, getting down now to the heart of the matter: what specifically are the core components of the mathematical theory of rTMS-induced neural plasticity articulated in this issue by Ma et al. (2025), and what is its relation to similar models proposed in the recent literature? As to the core model components: the first thing needed is some model of neural activity. This may be specified at the level of a population-average firing rate in a simple circuit of one, two, or more neural populations (Fung & Robinson, 2014; Wilson et al., 2018); or at the level of a single class of receptors (N-Methyl-D-Aspartate [NMDA] here) that are primarily responsible for plasticity-related changes (Huang et al., 2011; Ma et al., 2022, 2025). The synaptic strengths in this circuit are the principal object of interest – specifically whether they are enhanced or suppressed following the *in silico* rTMS protocol administration. Next, the stimulation: current is injected into one or more populations in the circuit, or activity of the key receptor types are modulated directly, according to the specific rhythmic pattern of the rTMS protocol of interest. Last but by no means least: plasticity. A key component of this class of theory is the empirical observation that fluctuations in intracellular calcium are the proximal causes of the positive/negative modifications to synaptic weights. Moreover, the relationship between intracellular calcium levels and plasticity is nonlinear and non-monotonic – such that low levels of intracellular calcium have no effect, intermediate levels induce LTD, and high levels induce LTP. The approach taken by Robinson, Fung and Wilson, based on the original formulation of Shouval, to describing this non-monotonic effect of calcium is to implement a single biphasic calcium response function, known as the 'omega function', which resembles an inverted upper-case Greek Omega (with the right-side leg taller than the left-side leg). In contrast, Ma et al. follow Huang et al.'s approach of proposing separate interacting 'inhibitory and facilitatory substances' (termed [Inhi] and [Faci]), which are respectively responsible for tendencies towards LTD- and LTP-like effects. These two substances compete and interact, with the ultimate plasticity outcome being a net effect of the two. As argued by Ma et al., the postulation of two separate, interacting, and competing substances has a stronger rationale in basic biochemistry than the single omega function. Relatedly, a notable further update of Ma et al's model over Huang's earlier version is the use of Michaelis-Menten (MM) kinetics to describe competing TMS-induced calcium signalling cascades. MM kinetics are a standard formalism in mathematical biochemistry used for enzyme-catalyzed reactions where one substance (the substrate) is transformed into another (the product). [Inhi] and [Faci] in this context are understood as enzyme-like factors that promote or suppress the conversion of the TMS input to a synaptic change. For both the omega function and the MM kinetics approaches, calcium levels oscillate slowly due to the interaction between external stimulation (TBS pulse trains), calcium decay dynamics, and the cumulative history of stimulation. Importantly, as noted in Ma et al. (2025)'s new results, and also earlier in Fung et al. (2014) and Wilson et al. (2018), it is the slow oscillation between LTD- and LTP-inducing calcium regimes that provides a potential explanation for plasticity sign-reversal effects observed by Gamboa et al. (2010) when comparing standard iTBS with 600 vs. 1200 vs. 1800 pulses. An important extension of the plasticity formulation in both the Ma and the Fung models is the inclusion of metaplasticity – a time- and state-dependent variation in the magnitude of the plasticity effect, using an adaptive sliding threshold approach to synaptic modification first introduced by Bienenstock, Cooper, and Munroe, generally known as 'BCM metaplasticity' theory (Abraham, 2008; Bienenstock et al., 1982). BCM or BCM-like components are incorporated in slightly different ways by Ma et al. than by Fung et al., but the overall effects are comparable: metaplasticity influences the amplitude, persistence, or damping (but not the emergence and existence) of calcium oscillations, particularly in prolonged stimulation

protocols.

In addition to the core plasticity model, Ma et al. follow Huang et al. in including a non-monotonic three-phase after-effect equation, which captures the empirically established progressive rise, preservation, and and decay of plasticity effects over ~50 min after completion of the rTMS stimulation. To accurately capture the time-course after-effect, Ma et al. aggregated the reported magnitudes and times of MEP effects from a large number (>60) of published iTBS and cTBS experiments, and fitted their model to this data using a novel parameter estimation approach. In doing so, their model shows an impressive ability to capture the time courses of LTP-like and LTD-like plasticity effects across a range of dosages (number of pulses).

An interesting and open question for future work remains what the underlying biological substrate of these after-effect dynamics, as well as other components such as their hypothesized [Inhi] and [Exci] substances themselves, might be. An ever-instructive comparison in this regard is none other than the Nobel prize-winning work of Hodgkin and Huxley (1952), whose mathematical theory of action potential generation developed during the 1940s and 1950s continues to underpin much of present-day neurophysiology. At that time, there was a good deal known from experimental recordings about properties such as neuronal resting potentials, voltage-dependence of membrane conductance, and its principal ionic drivers (sodium and potassium). However, in developing their model, Hodgkin and Huxley had to posit the existence of several (at the time) abstract quantities, such as time-varying ion channel gating variables with a particular mathematical form (cubic and quartic activation kinetics). It was in fact only decades later that the biophysical substrate of the voltage-dependent ion channel gates hypothesized by Hodgkin and Huxley were identified, first with patch clamp recordings in the 1970s (allowing direct measurement of currents through individual ion channels), and subsequently in the 1990s with X-ray crystallography and electron microscopy (confirming the presence of a tetramic molecular ultrastructure in potassium channels, matching the Hodgkin-Huxley model's use of quartic activation terms). This (luminous) historical case study may be useful (and motivating) for Ma et al. and others as to what a process of scientific discovery might look like for the key phenomenological components of their model, such as their postulated [Faci]/[Inhi] substances. Unlike HH however, fortunately these questions (once we know what exactly they are) would most likely not need to wait for 40 years of biotechnology development for their answers.

In conclusion: the road towards an explanatory, predictive, and computationally usable mathematical theory of rTMS-induced neural plasticity is one that, for the most part, remains grassy and wanting wear. The article by Ma et al. (2025) is an important recent instalment in this line of work, which extends back almost 20 years – expanding considerably its evaluation across empirical datasets, developing the mathematical formulation, and offering new suggestions as to candidate biological substrates. As emphasized earlier, there is a deep need for rational approaches to the task of mapping the intractably large parameter space of TMS protocol variations, both for discovery of new approaches and for personalization/optimization of established ones. E-Field modelling (Thielscher et al., 2015) is another useful comparison point here, as this was also originally a somewhat niche computational/theoretical technique, that over the past 10–15 years has developed into what is now a standard, almost mandatory component of TMS research and rTMS treatment planning. Is a similar future on the horizon for mathematical models of rTMS-induced plasticity?

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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